International Journal of Epidemiology
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Vol. 21, No. 5
Printed in Great Britain

Familial Aggregation of Oesophageal Cancer in Yangcheng County, Shanxi Province, China

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Hu N (Department of Cell Biology, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, China), Dawsey S M, Wu M, Bonney G E, He L J, Han X Y, Fu M and Taylor P R. Familial aggregation of oesophageal cancer in Xangcheng County. *International Journal of Epidemiology* 1992; **21**: 877–882

Oesophageal cancer is the second most common cause of cancer death in China and is particularly prevalent in northern China. Genetic factors have been studied less than environmental factors in the aetiology of this disease. This study was conducted to evaluate familial aggregation of oesophageal cancer. All households in Yangcheng County were interviewed in 1979 to determine family history of oesophageal cancer. In 1989, vital status for all family members from three Yangcheng villages was determined and re-interviews were conducted among families who reported a positive family history of oesophageal cancer in 1979. Risk of oesophageal cancer was evaluated by comparing family and individual rates of oesophageal cancer during the 1979–1989 interval stratified by the number of family members with oesophageal cancer prior to 1979. More families with prior oesophageal cancer history reported new oesophageal cancer deaths during the follow-up period than families without prior history (19% versus 5%). Oesophageal cancer rates increased with increasing positivity of family history, and adjustment for other risk factors did not substantially alter this result. We conclude that these data provide evidence for familial aggregation of oesophageal cancer.

Oesophageal cancer is a very common disease in many areas of China, especially in the North.[1–3] A nationwide survey of mortality in 1973–1975 identified oesophageal cancer as the second most common cause of death in China.[2]

Yangcheng county, Shanxi Province, covers about 1968 square kilometres at the southern end of the Taihang mountain range. It has a population of about 360 000 people in 25 villages. The region is poor, the inhabitants are primarily farmers, and the primary dietary staple is wheat. In 1972 a survey showed that Yangcheng county had a crude oesophageal cancer rate of 149/100 000 for males and females combined, one of the highest mortality rates from oesophageal cancer in China. Between 1974 and 1983 23% of all deaths in the population of Yangcheng were due to oesophageal cancer.[4] In 1979, another cancer mortality survey in Yangcheng found that all oesophageal cancer cases occurred in just 8% of households, an observation that suggested a strong tendency toward familial aggregation.

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The inhabitants of Yangcheng have had poor transportation facilities and little access to the outside world for long periods of time. They share similar environmental conditions and may also have genetic characteristics which make them susceptible to certain environmental carcinogens.[4,5] Extensive research has been done on environmental factors related to oesophageal cancer,[3,6] but little attention has been given to genetic factors. Family studies may provide an important opportunity for studying genetic-environmental interactions in the aetiology of this disease.

The purpose of the present study was to confirm the existence of familial aggregation among oesophageal cancer cases in Yangcheng, to quantify the risk associated with varying degrees of family history positivity, and to examine the interaction of genetic and environmental factors in the development of this disease. This work was performed as a collaborative effort involving the Cancer Institute of Chinese Academy of Medical Sciences in China, the National Cancer Institute of the US, and the Fox Chase Cancer Center in Philadelphia, PA.

METHODS

Definitions

A household was defined as family members living together at a common location. Each household had an official head, called the householder, a title designated in the permanent residence booklet kept in

each household. For this study, a family was defined as containing four generations, namely: householders, their siblings, and their spouses (the third generation); the householder's parents, uncles, and aunts and their spouses (the second generation); the householder's grandparents (the first generation); and the children of the householders and the children of the householder's siblings (the fourth generation). Family members, therefore, included all known blood relatives of the householder. Because of the Chinese tradition of women leaving their parents after marriage and sometimes losing touch with them, some members from the householder's maternal side could not be contacted. In this study, complete data were collected for four generations from the householder's paternal side, but such information was available for only two generations from the maternal side. Because of the incompleteness of the maternal side data only the data from the paternal side of the householders were analysed here.

Survey in 1979

In 1979, a group of doctors from Shanxi province visited all householders in Yangcheng individually. Family trees were traced back to the generation of householders' grandparents (i.e. three generations) on both the paternal and maternal sides of the family. Data obtained in 1979 included information on village, number of people in the family, and name, sex, date of birth, and relationship to householder of each household member. For people who had died, the age, year, and cause of death were recorded.

In the 1979 survey, a total of 11 446 oesophageal cancer deaths were identified among the 81 388 households in the county.* Ninety-two per cent of the households had no oesophageal cancer deaths over the three generations examined. Death from oesophageal cancer was found in only 8% of the households in Yangcheng. Among the 6665 households with oesophageal cancer deaths, 3871 households had only one case per household and 2794 households (3.4% of all households in the county) had multiple cases.

Follow-up in 1989

In 1989, a follow-up study was conducted among householders from selected villages in Yangcheng county. Three villages (Xi He, Ba Jiao-Kou, Yin Zhuang) were selected because of their proximity to Yangcheng City. The oesophageal cancer death rates of these three villages were approximately in the middle of those for the entire county. Vital status in 1989 was determined for all members from all families from these three villages (N = 5039) and confirmed by death records and the cancer registry of the Yangcheng County Department of Health. In addition, all the 592 families from these three villages who had reported a positive family history in the 1979 survey were personally interviewed, and additional information was collected. Interviews were conducted by trained doctors using a structured questionnaire, and information was obtained on each family member, including name, sex, date and place of birth, relationship to the householder, genetic status (adopted, twin), marital status, whether or not inbred, occupation, smoking and alcohol use, diet (eating pickled vegetables or hot food), and history of oesophageal cancer. For all family members with a history of cancer, a medical history was obtained, including symptoms (difficulty swallowing, abdominal pain), type of cancer, age at diagnosis, year of diagnosis, manner of diagnosis (by recall, village doctor, or hospital), methods of diagnosis for those going to hospital (cytology, x-ray, or pathology), age at death, and year and cause of death.

Interviews were conducted in homes and the primary respondent was the householder, but typically most of the living household members were convened together for the interview. When people could not recall specific information about their grandparents (or other deceased family members) the data were regarded as missing.

Families were categorized by family history (our primary exposure variable) as identified in the 1979 survey, depending upon the number of family members on the paternal side who had died with oesophageal cancer prior to 1980. For family category purposes, oesophageal cancer deaths identified in the 1979 survey from the householder's maternal side and from among people who married into the family but had no children or were adopted into the family (i.e. were not truly blood relatives) were excluded. The families in group 1 had one, those in group 2 had two, and those in group 3 had three or more family members from the householder's paternal side who died with oesophageal cancer before 1980. Only family members who were alive in 1979 were considered in the follow-up study analyses presented here. As mortality was our endpoint, people diagnosed with oesophageal cancer before 1980 who died after the start of follow-up (N = 6) were included in the analytic cohort.

* The Chinese term 'hu' means household, and this is the term used to describe the units of observation in the articles by Li *et al*[3] and Wu *et al*[4] written in Chinese. When translated into English, however, this became family rather than household. We have used the correct translation (i.e. household) when referring to their results.

Statistical Considerations

The data were manually edited in Yangcheng; pedigrees were drawn in Beijing; and data were coded, transcribed onto coding sheets, and double-keyed and verified in the US. Differences between individual characteristics by family history were compared using the χ^2 statistic.[7] The proportion of families from each family history group with new oesophageal cancer deaths identified during the follow-up was compared as the difference between two proportions.[7] Person-years of follow-up were calculated beginning in January 1980 and continuing until the time of death or January 1990, whichever came first. Because only year of death was known (not day or month), all events were assumed to have occurred in the middle of the year. Statistical testing of the differences between oesophageal cancer rates was done by summing χ^2 values (calculated as the square of the difference between the observed and expected number of events, divided by the expected number) across the six age-specific categories. Multivariate risk estimates were based on Cox models[8] and came from the SAS PHGLM procedure with age modelled as a continuous variable; other variables were dichotomized.[9] Trend tests were performed with PHGLM using a single family history variable scored as 1, 2, or 3.

RESULTS

Table 1 shows the characteristics of the families in the interviewed study population by the number of oesophageal cancer deaths per family prior to 1980. Of the total of 10253 blood relatives born into these families prior to 1980, 64% were alive in 1979 and were followed for vital status and cancer incidence through 1989. The average number of living family members was similar for each of the categories of oesophageal cancer family history (1 = 11.5, 2 = 10.5, 3+ = 11.3).

TABLE 1 *Characteristics of families in the interviewed study population in Yangcheng County, China, by status in 1979*

Variable	Oesophageal cancer deaths per family prior to 1980			
	1	2	3+	All
No. of families by village				
Xi He	110	86	76	272
Ba Jiao-Kou	75	54	34	163
Yin Zhuang	66	42	49	157
Total	251	182	159	592
Total no. of family members	4238	3024	2991	10253
No. of family members alive in 1979	2881	1918	1802	6601
Average family size alive in 1979	11.5	10.5	11.3	11.2

Table 2 provides the general characteristics of individuals in the interviewed study population in Yangcheng County by family history status in 1979. Individuals in family history categories 2 and 3 were slightly older on average than those in category 1. Differences between categories were also found for pickled vegetable and hot food consumption.

Between 1980 and 1989 a total of 516 deaths occurred among the 6601 people in the interviewed study population, including 127 oesophageal cancer deaths. These 127 cases, from 12% of the total families of the three villages, represent 37% of the total of 347 oesophageal cancer deaths confirmed from these three villages over this time period.

Table 3 shows the number of families in the three study villages with oesophageal cancer deaths between 1980 and 1989 by family history status in 1979. Significantly more families with prior oesophageal cancer history reported new oesophageal cancer deaths during the follow-up period than families without prior history (19% versus 5%, $P_{(2)} < 0.001$), with a slight increase in incidence for each increasing family history category. In addition, the number of families with multiple cases showed a gradient by family history: among the 4447 families with no family history of oesophageal cancer prior to 1980, 220 new cases were reported from 219 families; among the families with 1 prior case, 42 new cases were reported from 41 families; among the families with 2 prior cases, 38 new cases were reported from 32 families; and among the families with 3 prior cases, 47 new cases were reported from 37 families.

Table 4 shows age-adjusted and relative rates for oesophageal cancer death over the follow-up period for families in the study villages by gender and family history status. For males, rates are 117% higher among individuals with a positive as opposed to negative family history, and a steadily increasing trend is seen with increasing family history positivity. For females, however, none of the rates are increased significantly above the reference (no family history), although people coming from families with a 3+ family history are nearly significantly higher ($0.05 < P_{(2)} < 0.10$). For males and females combined, rates among people with a positive family history are 55% higher than people with a negative family history.

As shown in Table 5, there is little difference between the two models (age- and multivariate-adjusted) for the relative risk estimates for oesophageal cancer death by family history status and the relative risks

TABLE 2 *Characteristics of individuals in the interviewed study population in Yangcheng County, China, by status in 1979*

Variable	Oesophageal cancer deaths per family prior to 1980 (no. alive in 1979)			
	1 (N = 2881)	2 (N = 1918)	3+ (N = 1802)	All (N = 6601)
Age (average in years in 1979)	31.8	33.2[d]	33.1[e]	32.6
Sex (% male)	50	51	49	50
Marital status (% married)[a]	80	82	83	82
Occupation (% each category)[a]				
Farmer	83	82	83	83
Factory worker	6	7	6	6
Office worker	3	4	3	3
Student	9	7	8	8
Smoker (% yes)[a]	22	25	23	23
Alcohol (% yes)[a]	8	8	9	8
Eat pickled vegetables (% yes)[a,b]	96	98	97	97
Eat hot food (% yes)[a,c]	78	86	84	82

[a] Data obtained in 1989
[b] χ^2 df 2, 13.28, $P_{(2)} = 0.001$
[c] χ^2 df 2, 60.51, $P_{(2)} < 0.001$
[d] $P_{(2)} < 0.05$ compared to reference group (family history = 1)
[e] $P_{(2)} < 0.001$ compared to reference group (family history = 1)

TABLE 3 *Number of families in the study villages with oesophageal cancer deaths between 1980 and 1989 by status in 1979*

Variable	Oesophageal cancer deaths per family prior to 1980				
	0	1	2	3+	1+
No. of families with oesophageal cancer deaths between 1980 and 1989	219	41	32	37	110
Total no. of families	4447	251	182	159	592
% families with oesophageal cancer deaths between 1980 and 1989	5%	16%[a]	18%[a]	23%[a]	19%[a]

[a] $P_{(2)} < 0.001$ compared to reference category (family history = 0)

increased monotonically with family history positivity in both models.

DISCUSSION

The purpose of this study was to confirm the existence of familial aggregation among oesophageal cancer cases in Yangcheng, to quantify the risk associated with varying degrees of family history positivity, and to examine the interaction of genetic and environmental factors in the development of this disease. Analysed by family (Table 3) our results show clearly that oesophageal cancer does aggregate in families. While the effect is most striking for families with 3+ prior cases, the percentage of families with just 1 prior case who experienced an interval oesophageal cancer death was over threefold higher than that of families with no prior history. Analysed by individuals (Tables 4 and 5) the positive association was present but less

pronounced. The strong positive association observed in the family data, comparing families with and without positive histories, could not be examined by individuals because only people from families with a positive history in 1979 were re-interviewed in 1989 and additional covariate information obtained.

TABLE 4 *Age-adjusted rates[a] and relative rates[b] for oesophageal cancer death between 1980 and 1989 for individuals in the study population by sex and family history status in 1979*

Variable	Oesophageal cancer deaths per family prior to 1980				
	0	1	2	3+	1+
Males					
No. of cases	133	32	27[c]	27[c]	86[c]
Age-adjusted rate	103.8	197.8	230.6	262.3	225.6
Age-adjusted relative rate	1.00	1.91	2.22	2.53	2.17
Females					
No. of cases	87	10	11[d]	20	41
Age-adjusted rate	81.3	48.6	79.3	141.1	85.4
Age-adjusted relative rate	1.00	0.60	0.98	1.74	1.05
All					
No. of cases	220	42	38[d]	47[c]	127[c]
Age-adjusted rate	93.7	115.8	144.1	186.9	145.0
Age-adjusted relative rate	1.00	1.24	1.54	1.99	1.55

[a] Rates are per 100 000 person years, adjusted to the age distribution of the 1988 Yangcheng County population (<30 years = 53%, 30–39 years = 18%, 40–49 years = 11%, 50–59 years = 9%, 60–69 years = 6%, 70+ years = 3%)
[b] Relative rates are age-adjusted rates for each exposure category relative to the age-adjusted rates for the reference category (family history = 0)
[c] $P_{(2)} < 0.001$ compared to reference category (family history = 0)
[d] $P_{(2)} < 0.05$ compared to reference category (family history = 0)

TABLE 5 *Multivariate relative risk estimates for oesophageal cancer death between 1980 and 1989 by family history status in 1979*

Model	No. of oesophageal cancer deaths per family prior to 1980	Relative risk	95% Confidence interval
Age-adjusted	1[b]	1.00	—
	2	1.16	0.75–1.80
	3+	1.38[c]	0.90–2.12
Multivariate[a]	1[b]	1.00	—
	2	1.12	0.72–1.74
	3+	1.49[d]	0.97–2.27

[a] Adjusted for age, sex, marital status, occupation, tobacco, alcohol, pickled vegetable use, and hot food use
[b] Reference category
[c] χ^2 for trend = 2.21, $P_{(2)} = 0.137$
[d] χ^2 for trend = 3.35, $P_{(2)} = 0.067$

None of the environmental risk factors we examined, except age and gender, were associated with oesophageal cancer risk in this population (data not shown). Nor did adjustment for these risk factors alter the risk of family history (Table 5). By inference, this suggests that genetic as opposed to environmental factors are the more important cause of oesophageal cancer in this population. The possibility remains that our measurement of environmental risk factors may not have been accurate or we may have missed relevant factors. Alternatively, the relatively small number of events observed and the lack of variation in many of the risk factors evaluated may have limited our ability to observe differences related to these factors.

The results of this study are consistent with previous observations from this and other high-risk populations in China, including the findings of male predominance among cases, an increased risk associated with a positive family history, and positive familial aggregation of cases.[5,10]

The overall relative rate comparing positive to negative family history in males was increased (relative rate = 2.17) whereas it was not in females (relative rate = 1.05). One explanation for this gender difference may be the smaller number of events for females which may have resulted in an inappropriately high rate in the negative family history category or inappropriately low rates in the positive family history categories. Underreported or misclassified cases, if differential by exposure category, could result in lower risk estimates for family history in females. Our anecdotal experience in this population suggests that females are less likely than males to report symptoms and thereby their cause of death is more likely to be classified as 'stomach disease', 'wasting', or 'unknown' than males. Despite the lack of a positive association overall for family history in females, within the positive families the relative rates increased with family history category in both sexes, with higher relative rates in females (3+ category divided by 1 category = $3+/1 = 141.1/48.6 \times 10^{-5} = 2.90$) than in males ($3+/1 = 262.3/197.8 \times 10^{-5} = 1.33$).

In summary, we found strong evidence for familial aggregation of oesophageal cancer that is arguably more consistent with genetic than with environmental aetiology. Future comparison of risk in blood and non-blood relatives living in common environments, as well as segregation analysis, should help us understand further the relative contributions of genetic and environmental factors in the aetiology of this disease, and indicate specific molecular genetic studies to confirm the genetic hypothesis.

ACKNOWLEDGMENTS

We wish to acknowledge Frederick P Li from the NCI for helpful suggestions in initiating this project, and Steve Scoppa and Susan Bavola from Information Management Services, Silver Springs, MD, for their assistance in data entry, data management, and programming for the statistical analyses performed.

REFERENCES

[1] National Cancer Control Office. *Investigation of Cancer Mortality in China*. Beijing: People's Health Publishing House, 1980.

[2] National Cancer Control Office, Nanjing Institute of Geography, *Atlas of Cancer Mortality in the People's Republic of China*. Beijing: China Map Press, 1980.

[3] Yang C S. Research on esophageal cancer in China: A review. *Cancer Res* 1980; **40:** 2633–44.

[4] Li G H, He L J. A survey on the familial aggregation of esophageal cancer in Yangcheng county, Shanxi province, In: Wu M and Neberg D W (eds). *Genes and Disease*. Proceedings of the First Sino-American Human Genetics Workshop. Beijing: Science Press, 1986, 43–47.

[5] Wu M, Hu N, Wang X Q. Genetic factors in the etiology of esophageal cancer and the strategy for its prevention in high-incidence areas in North China. In: Lynch H T, Hirayama T (eds). *Genetic Epidemiology of Cancer*. Boca Raton, FL: CRC Press, 1989; pp 188–202.

[6] Li J Y. Epidemiology of esophageal cancer in China. *Natl Cancer Inst Monogr* 1982; **62:** 113–20.

[7] Colton T. *Statistics in Medicine*. Boston, MA: Little, Brown and Company, 1974.

[8] Cox D R, Oakes D. *Analysis of Survival Data*. London: Chapman and Hall, 1984.

[9] SAS Institute Inc. *SAS User's Guide; Statistics, 1985 edn*. Cary, NC: SAS Institute, 1985.

[10] Li J Y, Ershow A G, Chen Z J, *et al*. A case-control study of cancer of the esophagus and gastric cardia in Linxian. *Int J Cancer* 1989; **43:** 755–61.

(Revised version received April 1992)